

AMENDMENT UNDER 37 C.F.R. §1.111  
U.S. Application 09/509,677

**REMARKS**

Claims 1-20 are all the claims pending in the application. New claims 21-25 are added herein and are directed to a method of masking the taste of an oral administration preparation. Support for the claim amendments and the new claims is found in the specification on page 5, lines 5-14; page 6, line 15 to page 8, line 5; and page 15, lines 15-17.

Claims 6-14 and claims 16-18 have been amended herein to remove improper multiple dependencies.

**I. Claim Rejections Under 35 U.S.C. § 112, 1<sup>st</sup> Paragraph**

Claims 1-20 were rejected under 35 U.S.C. 112, first paragraph, allegedly because the specification does not reasonably provide enablement for any drug with unpleasant tastes other than drug compounds listed in specification from page 6, line 15 to page 8, line 5. According to the Examiner, the specification does not enable any person skilled in the art to use the invention commensurate in scope with the claims.

The Examiner states that there is no adequate direction provided in the specification to indicate to one of ordinary skill in the art how to select other drugs with unpleasant tastes which would be suitable in the instant invention. Further, the Examiner states that the instant specification does not provide any working examples to point out how drugs with unpleasant tastes other than the compounds listed in the specification from page 6, line 15 to page 8, line 5 may be used successfully in the claimed invention.

The Examiner contends that it is well known in the art that structural differences in active compounds will impart different chemical, physical, and therapeutic properties to the same compounds. Therefore different drug compounds with unpleasant tastes, other than the ones

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listed in specification from page 6, line 15 to page 8, line 5, may be reasonably expected to yield a different result. Due to this unpredictability, it would prevent the skilled artisan from selecting a compound which may be termed a “drug with unpleasant taste” to retain the desired function of the instant invention to improve taste in the oral therapeutic preparation with sugar alcohols specified herein, without undue experimentation.

Applicants respectfully traverse the rejection and submit that the relevant inquiry in regard to the scope of enablement of the claims is whether one of ordinary skill in the art would be enabled to make and use the entire scope of the claimed invention without undue experimentation. The fact that experimentation may be necessary does not make it undue if such experimentation is common within the art.

The Examiner appears to rely on an alleged “unpredictability” in the art of structural differences in compounds which, according to the Examiner, may impart different chemical, physical and therapeutic properties to compounds with unpleasant taste and prevent the skilled artisan from selecting a drug compound with an unpleasant taste to retain the desired function of the instant invention to improve taste in oral therapeutic preparations with sugar alcohols.

Applicants submit that on page 5 of the specification lines 5-14, examples of compounds having an unpleasant taste within the scope of the invention are described as including compounds which have at least one basic group in its structure, an acid addition salt of the compound, a solvate of the compound, a solvate of an addition salt and the like. Further, the term “basic group” is defined as a primary amino acid group, a secondary amino acid group, a tertiary amino acid group, a quaternary amino acid group and the like. Therefore, Applicants

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submit that the specification provides sufficient guidance to one of ordinary skill in the art in view of the knowledge in the state of the art, to select a drug with an unpleasant taste as claimed based upon a common structural feature and as such the specification is enabling.

Additionally, there are at least eight factors which must be considered when determining whether a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. *See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The level of predictability in the art is only one factor and it is improper to conclude that a disclosure is not enabling based on only one factor.

In regard to the Examiner's statement that the specification does not provide working examples for drugs other than the compounds listed in the specification, Applicants submit that it is not necessary to provide examples in the specification for each and every possible or conceivable embodiment of the claimed invention. As long as the invention is sufficiently disclosed such that one of ordinary skill in the art would be able to practice it without undue experimentation, the claimed invention is enabled.

**II. Claim Rejections Under 35 U.S.C. § 112, 2<sup>nd</sup> paragraph**

On page 3, claims 1-20 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite.

**A. “Unpleasant Taste”**

The Examiner states that the expression “unpleasant taste” in claims 1-4, 6, 9-11, 13-14, and 19 is a relative term which renders the claims indefinite because it is not defined in the claims and the specification does not provide a standard for ascertaining the requisite degree of

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“unpleasant taste”. For this reason and because it is allegedly unclear what drugs are encompassed by the claims, the Examiner concludes that one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Applicants respectfully traverse the rejection and submit the fact that claim language includes relative terminology does not necessarily render a claim indefinite. The proper inquiry is to first determine whether the specification provides some standard for measuring degree and second whether one of ordinary skill in the art would understand what is claimed in light of the specification. In this case, “unpleasant taste” is defined in the specification on page 1 as “a bitter taste, a sharp taste, a puckery taste and the like”. Throughout the specification it is indicated that the invention is directed at masking particularly bitter tastes which is also defined in the specification on page 5, lines 5-10. Further the Examples provide a standard for ascertaining the degree of bitterness based upon the results of the sensory tests carried out judging the degree of bitterness ranging from no bitterness, to bitterness strongly. In view thereof, Applicants submit that one of ordinary skill in the art would sufficiently be apprised as to the scope of the invention.

However, in an effort to facilitate and expedite prosecution, and not for reasons of patentability, the claims have been amended to recite “a drug having at least one basic group in its structure, thereby rendering an unpleasant taste” to more clearly define the claimed invention. In view thereof, Applicants respectfully request withdrawal of the rejection.

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**B. “Bitter taste”**

The Examiner states that the expression “bitter taste” in claim 2 is a relative term which renders the claim indefinite because it is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention and it is unclear as to what drugs are encompassed by the claims.

Applicants respectfully traverse the Examiner’s rejection and submit that the term “bitter taste” is defined in the specification on page 5, lines 5-10. Further the Examples provide a standard for ascertaining the degree of bitterness based upon the results of the sensory tests carried out judging the degree of bitterness ranging from “no bitterness” to “bitterness strongly”. In view thereof, one of ordinary skill in the art would sufficiently be apprised as to the scope of the invention.

**C. “Corrective Agent”**

The Examiner states that the term “corrective agent” in claims 16 and 20 renders the claims indefinite as to what agents are encompassed by the claims.

Applicants respectfully submit that on page 15 , lines 15-17, of the specification, examples of suitable corrective agents are provided. The specification is amended herein to correct an inadvertent error in translation. In view, thereof, Applicants respectfully request withdrawal of the rejection.

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**D. “Taking Ability”**

The Examiner states that the expression “taking ability” in claims 19 and 20 is not understood because it appears that Applicants’ invention is directed to a method of improving (masking) tastes of an oral preparation. The Examiner states that an amendment to this effect would be favorably considered.

The claims have been amended herein in accordance with the Examiner’s suggestion in order to facilitate prosecution of the application and not for purposes of patentability. Accordingly, Applicants respectfully request withdrawal of the rejection.

**III. Claim Rejections Under 35 U.S.C. § 102**

Claims 1-7, 9,12-14,16-18 were rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Pearmain (US Patent 5,188,839).

According to the Examiner, Pearmain teaches a cimetidine tablet, with improved palatability, that contains sodium bicarbonate, sorbitol and a sweetener aspartame (See particularly the abstract, col. 4, example 3). The Examiner further states that Pearmain also teaches the ratio between sorbitol and cimetidine is about 3.5 to 1 and the ratio between sodium bicarbonate and cimetidine is about 0.9 to 1. (See particularly col. 4, example 3).

Applicants respectfully traverse the rejection and submit that Pearmain does not teach or disclose the claimed property of a sugar alcohol having a dissolution of -20 cal/g or less and that the drug in the composition disclosed by Pearmain, cimetidine, is granulated with a particular amount of a particular polymethylacrylate copolymer to form a granule which is palatable and

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has good dissolution characteristics, see col. 2, lines 22-25, which appears to be a critical feature of the disclosed composition of Pearmain.

In order for a claim to be anticipated, each and every claim element must be taught in a single reference. As noted above the cited reference does not teach the quality of a sugar alcohol having a dissolution of -20 cal/g as presently claimed. Specifically, Pearmain does not teach a taste masking oral administration preparation consisting essentially of a drug having at least one basic group in its structure, thereby rendering an unpleasant taste, a sugar alcohol having a heat of dissolution of -20 cal/g or less and a pH adjusting agent or a method for masking the taste of an oral administration preparation as presently claimed. Accordingly, Applicants respectfully request withdrawal of the rejection.

**IV. Claim Rejections Under 35 U.S.C. § 103**

Claims 8, 10-11, 15, 19 and 20 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Pearmain (US Patent 5,188,839) in view of Hoshino (WO 97/1 2606, English equivalent, US Patent 6,146,661, is also provided).

According to the Examiner, Pearmain teaches a cimetidine tablet, with improved palatability, that contains sodium bicarbonate, sorbitol and a sweetener (aspartame). The Examiner states that Pearmain does not expressly teach (1) that erythritol, the sugar alcohol, is in the cimetidine tablet; (2) that the ratio between the sugar alcohol to cimetidine is from 5 to 10: 1; (3) that the pH values of the solution of the pH adjusting agent are equal to or higher than that of the solution of cimetidine; or (3) a method of improving “taking ability” employing the cimetidine tablet with improved palatability.

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To remedy the defects of Pearmain, the Examiner asserts that Hoshino teaches a chewable tablet that is free from unpleasant oral sensation which may contain a H<sub>2</sub> receptor blocking agent including cimetidine and erythritol. The Examiner further asserts that Hoshino also teaches a method of improving the unpleasant taste of the tablet with sugar alcohol herein, including erythritol (see col. 1 lines 51-58; col. 2, lines 25-56 particularly, and col. 6, line 1 to 60).

Thus, the Examiner reasons that it would have been obvious for one of ordinary skill in the art at the time the invention was made to employ the sugar alcohol, erythritol in the cimetidine tablet of Pearmain, with the ratio between the sugar alcohol to cimetidine being from 5 to 10:1 and the pH values of the solution of the pH adjusting agent equal to or higher than that of the solution of cimetidine and to employ the cimetidine tablet in a method of improving “taking ability”.

The Examiner states that one of ordinary skill in the art would have been motivated to incorporate erythritol into the cimetidine tablet of Pearmain because it is known in the art that erythritol is useful to improve unpleasant intrabuccal (oral) sensation in chewable tablet compositions. The incorporation of erythritol to improve the taste of a cimetidine tablet is therefore *prima facie* obvious.

The Examiner further states that optimization of result effect parameters (i.e., ingredient amounts, solutions, or suspension, pH values) is obvious as being within the skill of the artisan and that one of ordinary skill in the art would have been motivated to employ the cimetidine tablet of Pearmain as modified by Hoshino in a method of improving “taking ability” because the

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tablet would be expected to have improved taste and oral sensation and therefore the tablet would have been reasonably expected to be more pleasant to “take” or ingest orally.

Applicants respectfully traverse the rejection and submit that Pearmain does not teach or suggest the claimed invention for at least the same reasons set forth above. Further, Hoshino does not remedy the deficiencies of Pearmain and there is no suggestion or motivation to combine the references. In fact Hoshino is directed towards improving intrabuccal sensations, (discomfort such as roughness or dustiness in the mouth) characteristic of chewable tablets containing a gastrointestinal drug which remains in the mouth for a long time (see col. 1, lines 17-24). The improved effect is intrabuccal sensations and not taste. Namely, the features of Hoshino are not to improve the unpleasant tastes of drugs to such a degree that the unpleasant tastes are reduced or completely detectable, regarding the taking of oral administration preparations of drugs having unpleasant tastes which are dissolved completely or partially in the oral cavity before swallowing them, as in the present invention. On the other hand, the present invention is directed towards masking the taste of the active drug ingredient. Thus one of ordinary skill in the art would not have been motivated to combine the teachings of Pearmain and Hoshino with a reasonable expectation of arriving at Applicants’ claimed invention.

**V. The Present Invention**

The present invention has been achieved to improve the unpleasant tastes of drugs to such a degree that the unpleasant tastes are reduced or completely undetectable, regarding the taking of oral administration preparations of drugs having unpleasant tastes which have a possibility of the drug contacting directly with the oral cavity, e.g., powders, granules and tablets, in which

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film coating and the like is not carried out, and tables and granules which are quickly dissolved or disintegrated in the oral cavity.

The present invention is not directed to the case where drugs are made into pharmaceutical preparations as capsules, sugar coated tablets, film coated tables and the like dosage forms in order to mask unpleasant tastes of drugs at the time of their taking. That is, the present invention aims at improving the unpleasant tastes of drugs to such a degree that the unpleasant tastes are reduced or completely undetectable, regarding the taking of oral administration preparations of drugs having unpleasant tastes which are dissolved completely or partially in the oral cavity before swallowing them. The four Test Examples shown in the specification establish the unexpectedly superior effects of the present invention.

**VI. Differences Between the Claimed Invention and the Cited References**

As discussed above, the present invention is quite different from Pearmain in the oral administration preparation and the method for reducing the unpleasant tastes of drugs.

Further, as previously discussed Hoshino is directed to the improvement of the intrabuccal sensations characteristic to chewable tablets as compared to Pearmain which is directed to a technique of reducing the unpleasant taste of drugs. Thus one of ordinary skill in the art would not have been motivated to combine the teachings of Pearmain and Hoshino with a reasonable expectation of arriving at Applicants' claimed invention.

The methods for reducing the unpleasant tastes of drugs according to the present invention described on page 5, line 15 to page 8, line 14 of the specification, and particularly on

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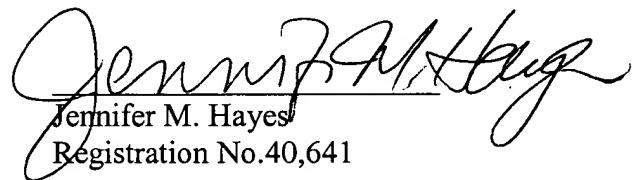
page 5, line 15 to page 6, line 14 of the specification are distinguishable from the cited references for at least the same reasons.

**VII. Conclusion**

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

Applicant hereby petitions for any extension of time which may be required to maintain the pendency of this case, and any required fee, except for the Issue Fee, for such extension is to be charged to Deposit Account No. 19-4880.

Respectfully submitted,



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**APPENDIX**  
**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**IN THE SPECIFICATION:**

**The specification is changed as follows:**

**On page 15, 1<sup>st</sup> full paragraph:**

Examples of the sweeteners include aspartame, stevia, thaumatin, saccharin sodium, dipotassium glycyrrhizinate and the like. Aspartame is particularly preferable among these sweeteners, because it has an effect to remove salty taste generated by the addition of a sodium salt as a pH adjusting agent. Aspartame is added in an amount of from 0.1 to 2% by weight, preferably from 0.05 to 1% by weight, more preferably from 0.1 to 0.5% by weight based on the total weight of the pharmaceutical preparation. Examples of the [correctives] corrective agents include L-menthol, camphor, mentha, monosodium L-glutamate monohydrate, dibasic sodium inosinate, magnesium chloride and the like. Among them L-menthol is particularly desirable, because it exerts a refreshing feeling and further increases the bitterness-improving effect. L-Menthol is added in an amount of from 0.01 to 2% by weight, preferably from 0.05 to 1% by weight, more preferably from 0.1 to 0.5% by weight, based on the total weight of the preparation.

**IN THE CLAIMS:**

**Claim 2 is canceled.**

**The claims are amended as follows:**

1. (Amended) A taste masking oral administration preparation [which contains] consisting essentially of a drug having [an unpleasant taste] at least one basic group in its

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structure, thereby rendering an unpleasant taste, a sugar alcohol having a heat of dissolution of -20 cal/g or less and a pH adjusting agent.

3. (Amended) The oral administration preparation according to claim 1 [or 2], wherein the drug [having an unpleasant taste] is a drug which has a bitter taste.

4. (Amended) The oral administration preparation according to [any one of claims] claim 1 [to 3], wherein the drug [having an unpleasant taste] is an H<sub>2</sub> blocker.

6. (Amended) The oral administration preparation according to [any one of claims] claim 1 [to 3], wherein the drug [having an unpleasant taste] is a mixture of one or more compounds selected from the group consisting of cimetidine, tranexamic acid and cetraxate hydrochloride.

7. (Amended) The oral administration preparation according to claim [any one of claims] 1 [to 6], wherein the sugar alcohol having a heat of dissolution of -20 cal/g or less is a mixture of one or more compounds selected from the group consisting of erythritol, xylitol, mannitol and sorbitol.

8. (Amended) The oral administration preparation according to [any one of claims] claim 1 [to 6], wherein the sugar alcohol having a heat of dissolution of -20 cal/g or less is erythritol.

9. (Amended) The oral administration preparation according to [any one of claims] claim 1 [to 8], wherein the sugar alcohol having a heat of dissolution of -20 cal/g or less is from 0.1 to 50 parts by weight based on 1 part by weight of the drug having an unpleasant taste.

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10. (Amended) The oral administration preparation according to [any one of claims] claim 1 [to 8], wherein the sugar alcohol having a heat of dissolution of -20 cal/g or less is from 5 to 10 parts by weight based on 1 part by weight of the drug [having an unpleasant taste].

11. (Amended) The oral administration preparation according to [any one of claims] claim 1 [to 10], wherein pH value of a 1% (w/v) aqueous solution or 1% (w/v) aqueous suspension of the pH adjusting agent is equal to or higher than the pKa value of the drug [having an unpleasant taste] or equal to or higher than the pH value of a 1% (w/v) aqueous solution or 1% (w/v) aqueous suspension of the drug.

12. (Amended) The oral administration preparation according to [any one of claims] claim 1 [to 11], wherein the pH adjusting agent is a mixture of one or more compounds selected from the group consisting of sodium bicarbonate, sodium dihydrogen phosphate anhydrous and precipitated calcium carbonate.

13. (Amended) The oral administration preparation according to [any one of claims] claim 1 [to 12], wherein the pH adjusting agent is from 0.1 to 200 parts by weight based on 1 part by weight of the drug [having an unpleasant taste].

14. (Amended) The oral administration preparation according to [any one of claims] claim 1 [to 12], wherein the pH adjusting agent is from 0.5 to 7 parts by weight based on 1 part by weight of the drug [having an unpleasant taste].

15. (Amended) A taste masking oral administration preparation [which contains] consisting essentially of an H<sub>2</sub> blocker, from 5 to 10 parts by weight of a sugar alcohol having a

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heat of dissolution of -20 cal/g or less and from 0.5 to 7 parts by weight of a pH adjusting agent, based on 1 part by weight of an H<sub>2</sub> blocker.

16. (Amended) The oral administration preparation according to [any one of claims] claim 1 [to 15], wherein it further contains a sweetener and/or a corrective agent.

17. (Amended) The oral administration preparation according to [any one of claims] claim 1 [to 15], wherein it further contains [aspartamine] aspartame and/or L-menthol.

19. (Amended) A method for[improving taking ability] masking the taste of an oral administration preparation [containing] comprising administering an oral administration preparation consisting essentially of a drug having at least one basic group in its structure thereby rendering an unpleasant taste, which is effected by including a sugar alcohol having a heat of dissolution of -20 cal/g or less and a pH adjusting agent.

20. (Amended) The method for [improving taking ability] masking the taste of an oral administration preparation according to claim 19, wherein a sweetener and/or corrective agent is further included.

**Please add the following new claims:**

21. (New) A method for masking the taste of an oral administration preparation in an oral cavity, comprising administering an oral administration preparation which comprises a drug compound which has a basic group in its structure, and increasing pH in the oral cavity to the pKa value or more of the drug using a pH adjusting agent in the oral administration preparation wherein the basic group is un-dissociated and wherein the solubility of the drug compound is reduced in the oral cavity.

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22. (New) A method for masking the taste of an oral administration preparation in an oral cavity, comprising administering an oral administration preparation which comprises a drug compound which has a basic group in its structure and changing the taste of the drug by increasing its solubility in fat.

23. (New) A method for masking the taste of an oral administration preparation in an oral cavity, comprising

administering an oral administration preparation comprising an amphoteric drug compound which has a basic and an acidic group in its structure,

increasing pH in the oral cavity to the pKa value or more of the acidic group in the structure using a pH adjusting agent in the oral administration preparation,

effecting dissociation of the acid group, and

forming an intramolecular salt or a salt of the pH adjusting agent.

24. (New) The method of claim 23 further comprising dissociation of the basic group.

25. (New) A method for masking the taste of an oral administration preparation in an oral cavity, comprising

administering an oral administration preparation which comprises a drug compound which is an acid addition salt of a compound which has a basic group or an acid addition salt of an amphoteric compound,

eliminating the acid addition salt and converting the drug into its free form using a pH adjusting agent in the oral administration preparation.